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EFFECTS OF KETAMINE, XYLAZINE, AND XYLAZINE-KETAMINE COMBINATIO--ETC(U)
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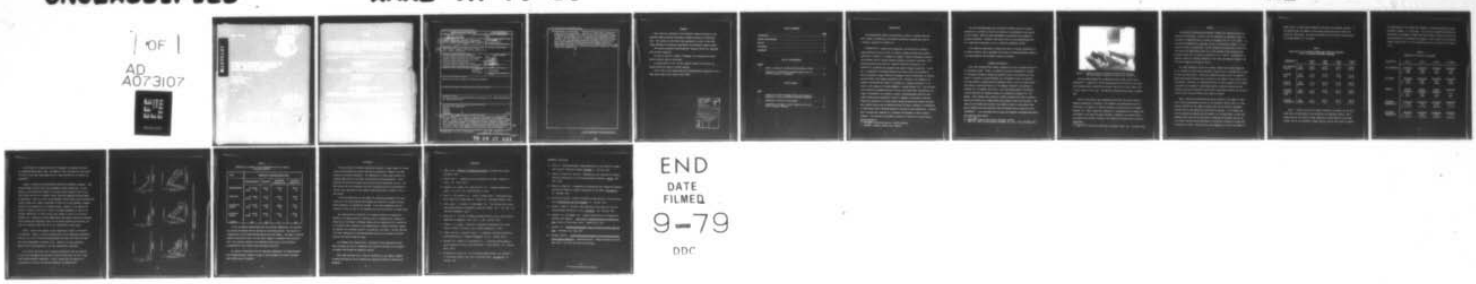

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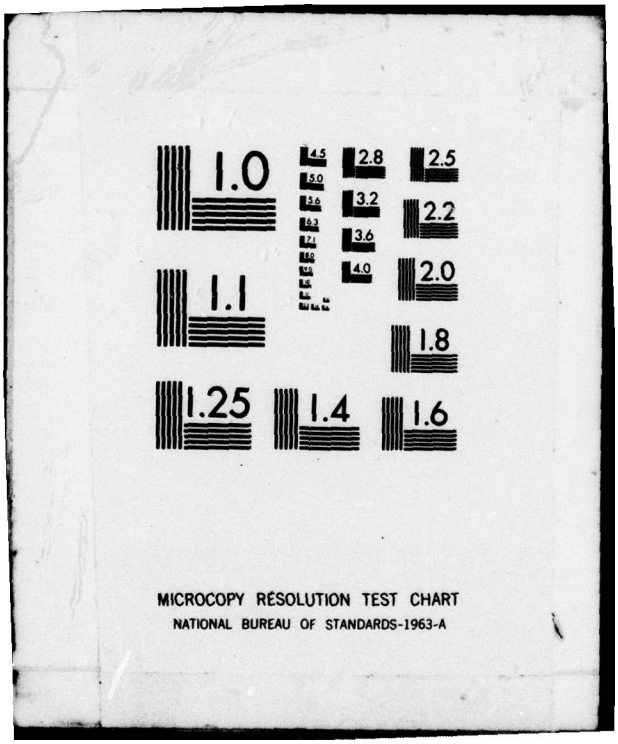
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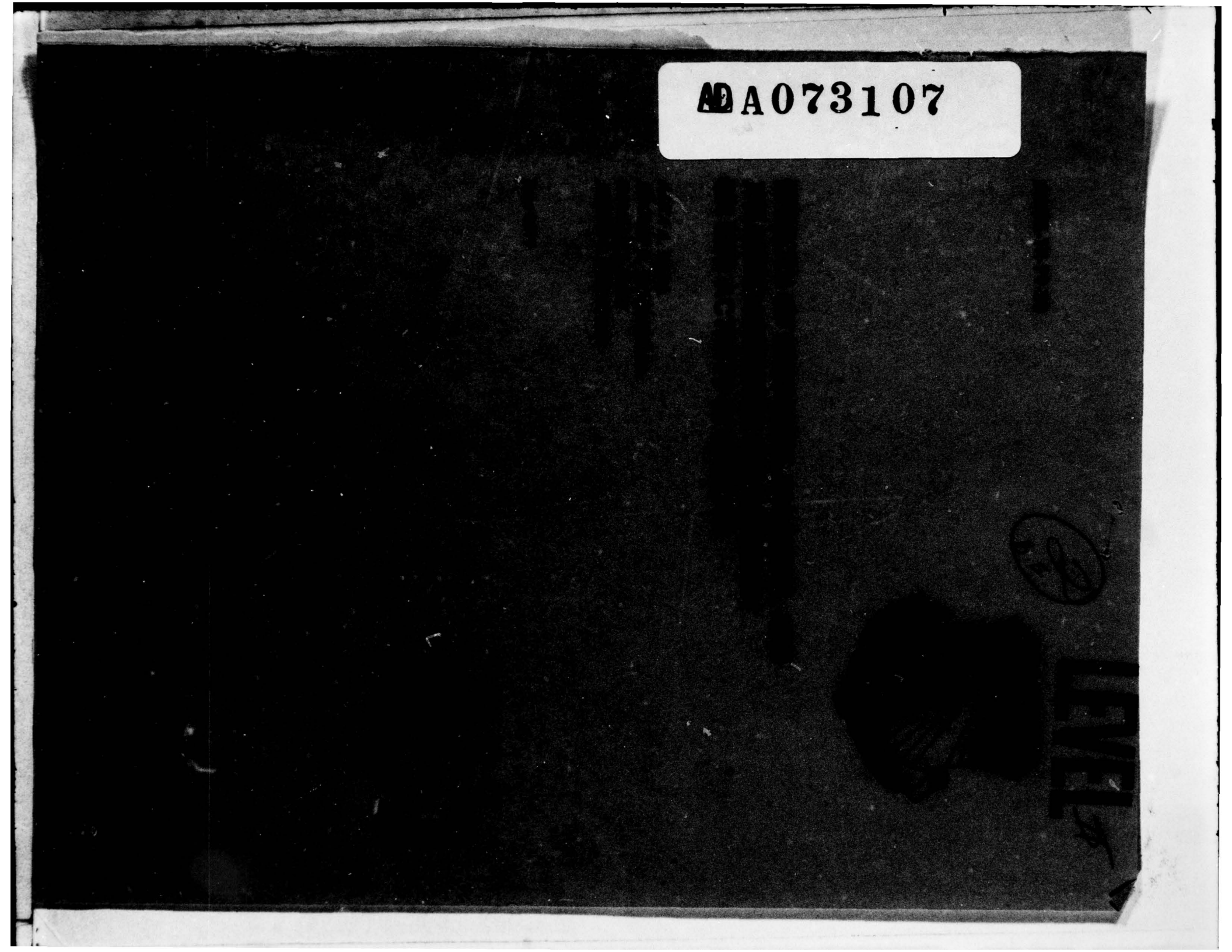

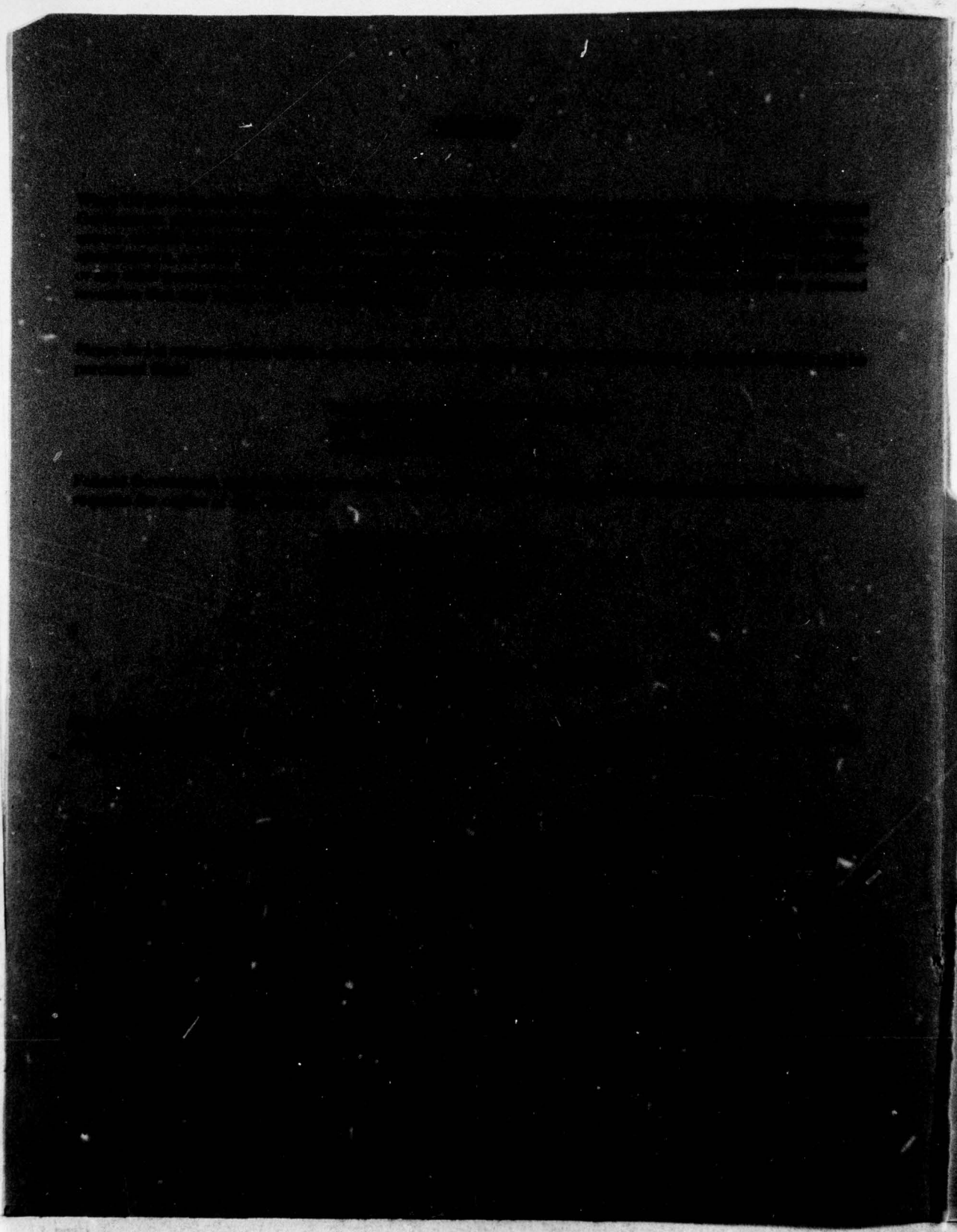

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Xylazine (~~Rompun~~ (R)) followed in 10 minutes with ketamine HCl (~~Vetalar~~ (R)) was found to be a safe, effective anesthetic combination in New Zealand White rabbits. Dosages of 8.8 mg/kg xylazine followed by 40 mg/kg ketamine produced light anesthesia/analgesia of approximately 45 minutes duration; dosages at the 9.9 mg/kg and 50 mg/kg level produced surgical anesthesia for approximately 75 minutes. EEG's, pain response, heart rates and rectal temperatures were monitored with both dose regimes and during several surgical procedures

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(laparotomy, toe amputation). The EEG activity was used to analyze the trend and level of anesthesia. Statistics of EEG activity during the preinjection, anesthesia and recovery periods were calculated. Changes in EEG are most prominent one to two minutes after administration of ketamine. At this time there is a large increase in the level of delta activity and a corresponding decrease in the alpha and beta activity. Heart rates decreased following xylazine and ketamine injections. Temperatures were noted to decrease with both combinations of these drugs. Pentobarbital anesthesia was similarly monitored for comparison; variable effects were observed.

PREFACE

This study was conducted in the Veterinary Sciences Division of the Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio. The results of this effort were presented, in part, at the 25th Annual Meeting of the American Association for Laboratory Animal Science.

The authors gratefully acknowledge Ms. Virginia Cornick for assisting with the data reduction.

We wish to thank Dr. Schmidl of Chemagro for furnishing the experimental xylazine used in this study.

Our appreciation to Dr. (Lt Col) Charles Lessard for allowing and demonstrating the usage of the EEG analyzer.

Alva A. Karl is now associated with Systems Research Laboratories, Inc., 2800 Indian Ripple Road, Dayton, Ohio 45400.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

INTRODUCTION

The unpredictable nature of barbiturates, wherein a standard dose may prove lethal or ineffective, can present significant problems when used as a surgical anesthesic in rabbits (1).

Ketamine HCL[1], a dissociative anesthesic, has been used in numerous animal species (2,3,4,5,6,7,8,9) and found to produce satisfactory surgical anesthesia in rabbits at a dosage of 44 mg/kg. Another investigator reported that Ketamine did not provide adequate analgesia and muscle relaxation, while Xylazine produced good sedation, analgesia and muscle relaxation, (11). Xylazine[2] is a sedative and analgesic with muscle relaxant properties. In the cat, a combination of Ketamine-Xylazine was found to have the advantage of muscle relaxation, longer duration of analgesia, and the maintenance of sedation during recovery from surgical anesthesia (12). Recently, the combination of Ketamine and Xylazine was shown to be useful as a surgical anesthetic in the rabbit at the dosage of 35 mg/kg Ketamine + 5 mg/kg Xylazine (13). The anesthetic state produced by Ketamine does not fit into the conventional classification of stages of anesthesia, but produces a state of unconsciousness which has been termed "dissociative anesthesia" in that it appears to selectively interrupt association pathways to the brain before producing somesthetic sensory blockade. Also skeletal muscle tone is variable and may be normal, enhanced, or diminished. At high dosage levels, Ketamine produces a decrease in body temperature. Xylazine, also a non-narcotic compound, is a sedative and analgesic as well as muscle relaxant. Its sedative and analgesic activity are related to central nervous system depression.

1. Vetalar®, Parke-Davis and Co., Detroit Michigan
2. Rompun®, Chemagro, Kansas City, Missouri

The electroencephalogram has been used in research aspects of general anesthesia as a method to describe the effects of depressants on the central nervous system. There has been considerable controversy on the nature of Ketamine anesthesia. Ketamine, when used in the cat, has been defined both as a dissociative anesthetic and as a stimulant anesthetic (14,15).

This study was undertaken to assess the effect of various anesthetics on the EEG of rabbits, and to determine the effects of Ketamine-Xylazine combination during general and orthopedic surgical procedures.

METHODS AND MATERIALS

Adult (New Zealand White) rabbits comprised the seven treatment groups in the anesthesia study. Group 1 (6 rabbits) were given Pentobarbital Sodium[3] iv (30 mg/kg) through an indwelling catheter placed in the lateral ear vein. Group 2 (2 rabbits) received Ketamine I.M. (50 mg/kg); Group 3 (2 rabbits) received Xylazine intramuscularly (8.8 mg/kg); Group 4, the "low dosage group" (10 rabbits) received Xylazine I.M. (8.8 mg/kg) followed in 10 minutes by Ketamine I.M. (40 mg/kg); and Group 5, the "high dosage group" (10 rabbits) received Xylazine (9.9 mg/kg) followed in 10 minutes by Ketamine I.M. (50 mg/kg). These rabbits were placed in a rabbit restraint box (Fig. 1) and two EEG pin electrodes and a common ground were placed in skin over the skull. Two other pin electrodes were placed on the rabbit's chest to record heart rate. Rectal temperatures were monitored every 10 minutes with an electronic telethermometer[4]. All electrodes were in place and baseline recordings made before any injections were given.

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3. Nembutal®, Abbott Laboratories, Chicago, Illinois
4. Model No. 46TUC, Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio

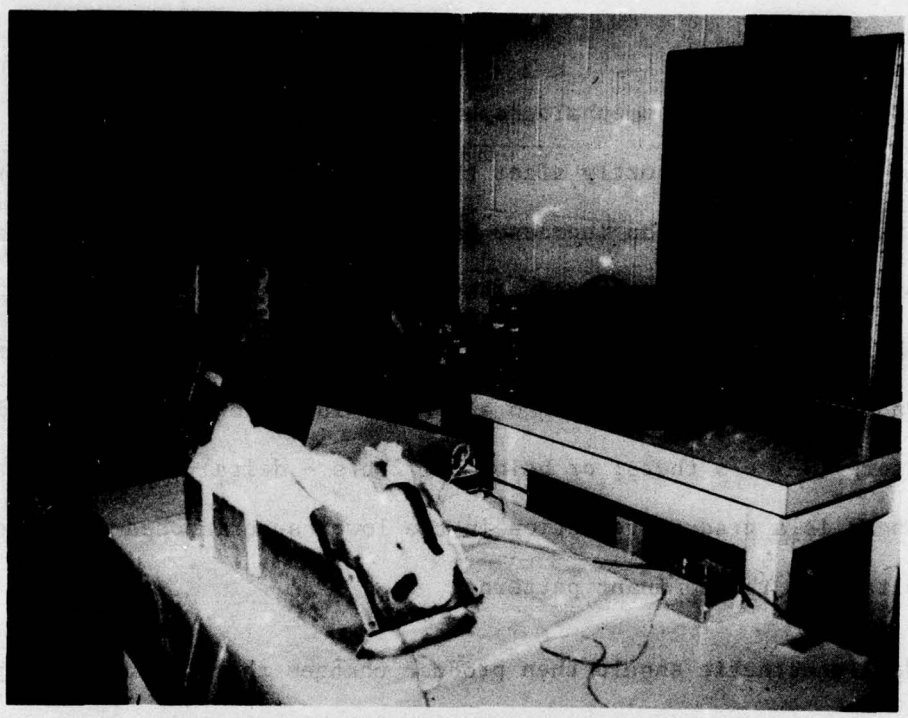

Figure 1. Rabbit in Restraint System with Electrodes in Place
Note EEG Coupler, Analyzer and Recorder in Background.

Electroencephalography was accomplished using an EEG coupler with a preamplifier [5] connected to an EEG sleep analyzer (16,17,18) with the brain wave frequency bands classified as follows: Delta (0.5-3.5 H_z), Theta (3.5-7.5 H_z), Alpha (7.5-12.5 H_z). The EEG data obtained was recorded on digital tape.

Group 6 (six rabbits) were anesthetized with the "low dose" Xylazine-Ketamine combination, and Group 7 (six rabbits) were anesthetized with the "high dose", 9.9 mg/kg I.M. Xylazine followed 10 minutes later by 50 mg/kg Ketamine I.M. These animals were subjected to laparotomies with clamping and stretching of the large and small intestine, clamping of the uterine horns and ovaries with forceps, closing of the incision, and from three to five toe amputations.

5. Model No. 11-4307-02 and Universal 13-4218-00, Gould, Inc., Cleveland, Ohio

RESULTS

The pattern of electroencephalographic changes with anesthesia have been described as follows (1): Shortly after the induction of anesthesia, there is a decrease in amplitude and an increase in frequency (20 c/s - beta waves). As the depth of anesthesia is increased, there is a progressive change to a lower frequency (8-12 c/s alpha wave). As the anesthetic concentration is increased, this pattern of alpha waves fades into a more dominant lower frequency high voltage pattern (4-7 c/s theta; or below 3 1/2 c/s - delta). As anesthesia is deepened, there is a gradual reduction in the lower superimposed frequency and the high voltage is the dominant pattern.

The ideal anesthetic should then produce changes that could be analyzed by an increase in alpha during anesthesic induction with a concommitant increase in theta and delta waves. During the anesthetic period itself, the numbers of alpha waves should decrease and an increase in the number of delta waves should be observed. Therefore, if Pentobarbital were an ideal anesthetic in the rabbit, a decrease in the number of alpha waves should be observed between the pre-injection period and anesthetic period with a significant increase in the number of delta waves observed between these same two periods.

Table 1 shows that although there was an increase in the number of delta waves from the preanesthetic period to the anesthetic period, there is a significant increase in the number of alpha waves for the same two anesthetic periods which is the opposite of what would be expected. If we compare the same two anesthetic periods (pre and anesth.) in the same Table, we find that Ketamine alone, and the two dose rates of Ketamine and Xylazine function as true central nervous system depressants in producing a decrease in alpha with an increase in delta. Xylazine alone at 8.8 mg/kg did not alter the number of

alpha, theta, or delta waves observed for the same two anesthetic periods. It was expected that the number of theta waves would follow more closely the pattern of alpha waves. We can only speculate that this may be characteristic of the EEG analysis of the rabbit.

TABLE 1

COMPARISON OF EEG RECORDINGS BEFORE AND DURING THE ANESTHETIC PERIOD OF DIFFERENT ANESTHETIC REGIMENS

ANESTHETIC		DELTA CPS	THETA CPS	ALPHA CPS	F CROSS CPS
PENTOBARBITAL 30mg/kg	PRE	65.08	373.75	114.00	793.58
	ANESTH	138.88	188.58	136.17	688.95
KETAMINE 50mg	PRE	34.90	234.60	136.40	1217.20
	ANESTH	114.20	111.70	71.60	449.80
ROMPUN 8.8mg/kg	PRE	61.10	296.50	145.10	1045.00
	ANESTH	64.40	344.70	147.30	973.30
KETAMINE + ROMPUN (LOW)	PRE	57.10	299.90	155.13	992.90
	ANESTH	146.80	77.33	46.75	406.43
KETAMINE + ROMPUN (HI)	PRE	74.24	269.51	146.14	962.34
	ANESTH	166.38	90.53	48.13	424.02

Table 2 reflects the type of change (increase or decrease) for all wave forms that occurred between the preinjection and anesthetic period. The t values indicate the relative change (negative t values indicate an increase between the pre and anesthetic stages) and the p value can be used to compare

the significance of the change when compared or evaluated against any other anesthetic regimen. It can be seen that there was a significant difference (decrease) in the number of alpha waves and increase in delta waves with the Xylazine-Ketamine low and high dose regimens. The t values for the Xylazine regimen indicate that it did not significantly alter the wave form frequency at all.

TABLE 2

COMPARISON OF EEG WAVE FORM CHANGES

ANESTHETIC	DELTA	THETA	ALPHA	F CROSS
PENTOBARBITAL	INCREASE t= -2.80 p= .0189	DECREASE 3.80 .0035	INCREASE -.66 .5218	DECREASE 1.29 .2264
KETAMINE	INCREASE t= -6.69 p= .0216	DECREASE 6.05 .0263	DECREASE 2.91 .1008	DECREASE 8.39 .0139
ROMPUN	SLIGHT INCREASE t= -.22 p= .8472	SLIGHT INCREASE -1.68 .2354	SLIGHT INCREASE -.14 .9010	DECREASE 4.21 .0521
KETAMINE ROMPUN (LO)	INCREASE t= -11.05 p= $.02 \times 10^{-6}$	DECREASE 8.47 $.71 \times 10^{-5}$	DECREASE 6.98 $.38 \times 10^{-4}$	DECREASE 6.17 $.11 \times 10^{-3}$
KETAMINE ROMPUN (HI)	INCREASE t= -8.17 p= $.18 \times 10^{-6}$	DECREASE 8.29 $.15 \times 10^{-6}$	DECREASE 4.06 $.73 \times 10^{-3}$	DECREASE 7.19 $.108 \times 10^{-5}$

The reliance on a single wave form or frequency to determine the depth of anesthesia may be misleading. The number of zero crossings per time period (F cross) of all wave forms appears to be a more accurate way to evaluate an anesthetic.

Figure 2 illustrates the differences between the anesthetic regimens. Here the percentage of delta's two zero crossings is shown versus time. In this manner, we can analyze the number of F crosses (total crosses of zero by all wave forms) into the one component, delta, that more regularly portrays depth of anesthesia. There is a very low percentage of delta waves in the unanesthetized control animal and a higher percentage of deltas in all the anesthetic regimen groups with the exception of the Xylazine group. However, if we combine the percent of deltas in the total F cross of Xylazine anesthesia to that of the Ketamine anesthesia, we find a picture more similar to that of the Xylazine-Ketamine mix. Therefore, we have demonstrated that neither Xylazine or Ketamine alone produced the anesthesia effect of the mixture Xylazine and Ketamine, but that the anesthetic effect was due to the combination of these drugs.

Table 3 reflects the changes in body temperature related to the period of anesthesia. There is a more pronounced drop in body temperature associated with the use of the low dose Xylazine-Ketamine mix than with either the high dose Xylazine-Ketamine or Xylazine alone. However, all three produced a greater drop in body temperature than the pentobarbital anesthesia.

It was noted that heart rates decreased approximately 25% and remained at this level throughout the anesthetic periods using either the low or high dose Xylazene-Ketamine combination. Group 1 showed just the opposite by increasing heart rate by 25% when pentobarbital was administered.

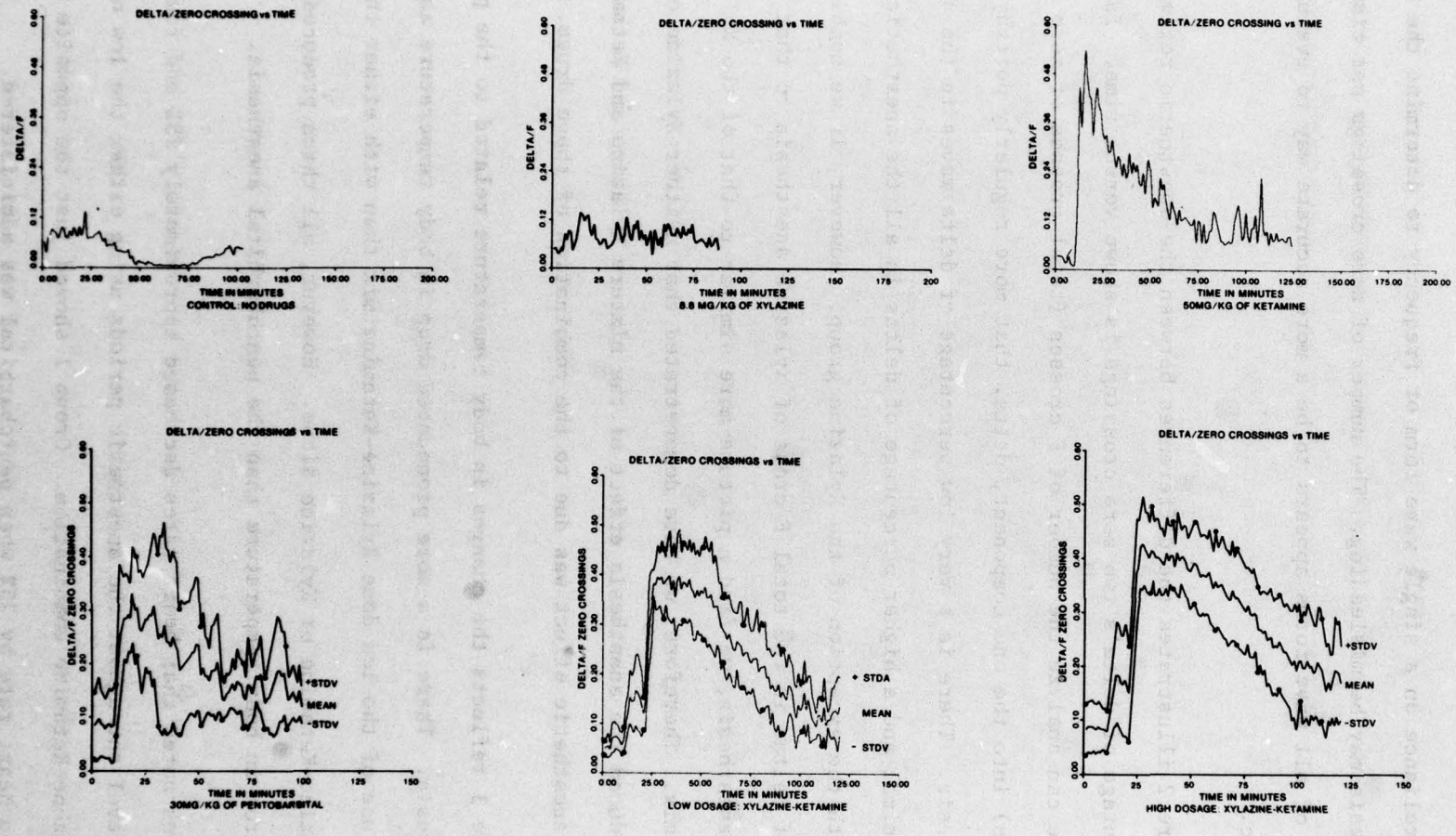

Figure 2. Comparison of Delta/Zero Crossings versus Time for Anesthetic Treatments

TABLE 3

COMPARISON OF CHANGES IN BODY TEMPERATURE WITH THE VARIOUS REGIMENS EMPLOYED

TIME	ANESTHETIC REGIMENS EMPLOYED			
	PENTOBARBITAL	ROMPUN	KETAMINE ROMPUN (LOW)	KETAMINE ROMPUN (HI)
PREINJECTION	$\bar{X}$= 38.99 STDV= .26	39.25 .07	39.40 .21	39.28 .42
INJECTION	$\bar{X}$= 38.99 STDV= .27	39.15 .07	39.14 .28	39.25 .40
ANESTHETIC PERIOD	$\bar{X}$= 38.89 STDV= .32	38.80 .26	38.03 .83	39.01 .33
RECOVERY PERIOD	$\bar{X}$= 38.50 STDV= .47	38.30 .14	37.70 .64	38.38 .40
CHANGE*	-.49	-.95	-1.7	-.90

Of the six rabbits anesthetized with the low dose combination, two tolerated the surgical procedures with no reaction to pain being noticed. One reacted to clamping down on the uterus fifteen minutes into the surgery. One rabbit tolerated abdominal manipulation well, but did react slightly to abdominal skin suturing. Two of the subjects reacted to toe amputation which was the last procedure accomplished at fifty minutes after anesthetic induction.

Six rabbits anesthetized with the high dose combination (9.9 mg/kg Xylazine and 50 mg/kg Ketamine) showed no signs of pain throughout the entire procedure which lasted about 55 minutes.

DISCUSSION

The EEG analysis of Ketamine anesthesia indicated a slight degree of central nervous system depression, while there was no significant changes in the EEG produced by Xylazine anesthesia. The combination of these drugs produced the classical EEG picture of an ideal central nervous system depressant. Pentobarbital was used as the model central nervous system depressant control. The EEG picture with this anesthetic was only confusing and may be attributable to the fact that anesthesia in the rabbit using barbiturates is either an all or none effect.

It was determined that in the rabbit the anesthesia produced by the combination of the drugs Xylazine and Ketamine was identical to central nervous system depression as analyzed by the EEG. It was also determined that the anesthetic effect was due to the combined action of both and not to either alone.

The administration of Xylazine at 9.9 mg/kg followed in 10 minutes by Ketamine at 50 mg/kg produced a suitable level of anesthesia that allowed for clamping and stretching of abdominal organs and toe amputations for a period up to 55 minutes after induction, thus demonstrating a reliable anesthetic regime for general and orthopedic surgical procedures in the rabbit. We feel that the "low dose" combination of Xylazine-Ketamine would only be adequate for short duration and limited surgical usage.

Our findings also indicated that a decrease in body temperature occurs when the drugs are used in combination that should be counteracted by keeping the animal warm during the anesthetic period.

This study indicates that a state of anesthesia in the rabbit, adequate in depth and duration can be achieved with appropriate doses of Xylazine and Ketamine.

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